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Arterial hypotension in chronic hemodialyzed patients

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We studied in 32 patients on maintenance hemodialysis (duration of treatment 6 to 133 months) whether duration of dialysis treatment affects blood pressure, plasma noradrenaline levels and α_2-adrenoceptor density (assessed in platelet membranes by ^{3}H-yohimbine binding). Plasma noradrenaline levels were a significant inverse correlation to platelet α_2-adrenoceptor density. In addition, mean arterial blood–pressure, plasma noradrenaline levels and platelet α_2-adrenoceptor density were significantly related to the duration of treatment: with increasing duration of treatment plasma noradrenaline levels increased, whereas mean arterial blood–pressure and platelet α_2-adrenoceptor density decreased. Furthermore, changes in mean arterial blood–pressure were inversely related to plasma noradrenaline levels and positively to platelet α_2-adrenoceptor density. Platelet α_2-adrenoceptor changes were accompanied by similar alterations in (vascular) α_1-adrenoceptor responsiveness (assessed by blood pressure responses to i.v. injections of phenylephrine); in hypotensive hemodialysis patients, who had high, plasma noradrenaline levels and low, platelet α_2-adrenoceptor density, the dose of phenylephrine necessary to increase systolic blood pressure by 20 mm Hg was nearly twice as high as in normotensive dialysis patients and healthy controls. In autonomic tests, Valsalva–ratio was lower in hypotensive than in normotensive dialysis patients and healthy controls, whereas no differences were found in blood pressure and heart rate responses during sustained hand–grip exercise as well as in beat–to–beat variation during deep breathing. It is concluded that with increasing duration of the dialysis treatment, pathological changes in mean arterial blood–pressure, plasma noradrenaline levels and platelet α_2-adrenoceptor density increase; moreover, in the course of long–term treatment, baroreceptor dysfunction develops obviously due to a defect in the afferent limb of the baroreflex arc. The (possibly to this baroreceptor dysfunction reflectorily) increased plasma noradrenaline levels may induce α-adrenoceptor down–regulation. The resulting reduction in α-adrenoceptor responsiveness to α-adrenergic stimuli (including endogenous catecholamines) might be one important cause of arterial hypotension in patients on long–term hemodialysis treatment.

Abnormalities of autonomic control of the cardiovascular system have been frequently observed in patients with chronic renal insufficiency undergoing hemodialysis [1, 2]. Reduced baroreceptor sensitivity [3], abnormal responses to the Valsalva maneuver [4], dialysis–induced hypotension [5, 6] and elevated plasma noradrenaline levels [7–9] have been reported. In addition, blood pressure response to noradrenaline infusion was found to be markedly attenuated in patients on maintenance hemodialysis, suggesting an impaired (vascular) α-adrenoceptor function [5]. In animal models of experimental chronic uremia an attenuated α-adrenoceptor responsiveness (assessed as vascular response to noradrenaline infusion of the isolated, perfused rat hind limb) has as well been observed [10] and a decreased vascular α-adrenoceptor density was reported [11]. However, little is known on changes in the properties of α-adrenoceptors—the targets of catecholamines—in patients on maintenance hemodialysis. In the present study, we therefore determined the density of α_2-adrenoceptors in circulating platelets (by ^{3}H-yohimbine binding) and the responsiveness of (vascular) α_1-adrenoceptors (by blood pressure responses to i.v. injections of the selective α_1-adrenoceptor agonist phenylephrine) in 32 hemodialysis patients with a different duration of treatment (6 to 133 months) in order to find out whether in the course of long–term dialysis treatment similar changes in α-adrenoceptor function might occur as in experimental chronic uremia. In addition we determined plasma noradrenaline levels and studied autonomic function by three standardized cardiovascular autonomic tests (Valsalva–maneuver, sustained hand–grip exercise, and beat–to–beat variation during deep breathing) to evaluate whether the increase in plasma noradrenaline levels observed in patients on chronic hemodialysis treatment might be cause or consequence of possible changes in α-adrenoceptor function.

Methods

Thirty–two patients on maintenance hemodialysis (24 males, 8 females; mean age 48.5 ± 2.1 [24 to 69] years; duration of hemodialysis treatment 6 to 133 months) participated in the study after having given informed written consent. The causes of renal failure in the 32 patients were chronic glomerulonephritis in 15, polycystic kidney disease in 6, nephropathy due to analgesic drugs in 3, chronic pyelonephritis in 3, cortical necrosis in 1 and chronic renal failure of uncertain etiology in 4 patients. The development of interdialytic blood pressure of the patients in relation to blood pressure levels before initiation of dialysis treatment and duration of dialysis treatment is given in Table 1. All patients were not on antihypertensive therapy for at least three weeks. Medication consisted of calcium carbonate, sodium hydrogencarbonate, aluminium containing phosphate binding drugs, 1-alpha-hydroxyvitamin D_3, multivitamins and iron supplementation. Hemodialysis treatment was performed three times, five to six hours per week as standard acetate dialysis with additional infusion of sodium bicarbonate [12]. After 30 minutes of rest, blood pressure was measured by the auscultatory method (diastolic phase V) with the patients in sitting position. Blood pressure values are given as average of at least three measurements on separate days. Blood pressure was

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Table 1. Development of blood pressure in 32 patients on maintenance hemodialysis in relation to blood pressure levels before initiation of dialysis treatment and duration of dialysis treatment

Patients		After 1 year of dialysis				After 1 to 2 years of dialysis				After 2 or more years of dialysis			
		HT	BHT	NT	HOT	HT	BHT	NT	HOT	HT	BHT	NT	HOT
Hypertensive 1 to 5 yrs. before dialysis treatment until entry of treatment	11	3	1	6	—	—	1	8	1	—	—	4	3
Normotensive 1 to 5 yrs. before dialysis treatment, but hypertensive on entry of treatment	15	1	5	8	—	1	1	11	1	—	1	5	3
Normotensive until entry of dialysis treatment	6	—	—	6	—	—	—	6	—	—	—	3	1

Abbreviations are: HT, hypertensive; BHT, borderline hypertensive; NT, normotensive; HOT, hypotensive

measured and blood was always taken between 9.00 and 10.00 a.m., that is 10 to 20 hours after the last dialysis treatment. After 30 minutes of rest, 20 ml venous blood was withdrawn with the subjects in sitting position and anticoagulated by mixing 9 ml of blood with 1 ml of 3.2% sodiumcitrate solution. In addition 5 ml of blood were mixed with 50 μl of a solution containing 190 mg EGTA and 40 mg DTT per ml for determination of plasma catecholamines.

Platelet membrane preparation and ^{3}H-yohimbine binding assay was performed as recently described [13]. Briefly, membranes (approximately 50 to 100 μg of protein) were incubated with 6 to 8 concentrations of ^{3}H-yohimbine (ranging from 0.5 to 10 nmol/liter) at 25°C for 30 minutes in a total volume of 250 μl. Incubation was terminated by diluting the entire reaction mixture with 10 ml incubation buffer (50 mmol/liter Tris-HCl, 0.5 mmol/liter EDTA adjusted to pH 7.4 with 1.0 mmol/liter HCl) followed by rapid filtration over Whatman GF/C glass fiber filters. After drying filters were transferred to vials containing 5 ml of Unisolve (Zinsser, Frankfurt, FRG) as scintillation fluid and the radioactivity was determined in a Beckman LS 9000 liquid scintillation counter (Beckman Instruments, Fullerton, California, USA). "Non-specific binding" of ^{3}H-yohimbine was defined as binding to platelet membranes not displacable by 10 μmol/liter phentolamine. Under these experimental conditions the intra-individual variation of platelet α_2-adrenoceptor number was less than 15%.

Seventeen patients on maintenance hemodialysis and eight healthy volunteers participated in the phenylephrine study. The patients were divided into two age–matched groups: one group of hypotensive dialysis patients (4 males, 4 females) with relatively low, interdialytic blood pressure ($P_{syst} < 110$ mm Hg; blood pressure average 103.3 ± 2.8/72.5 ± 2.3 mm Hg; mean age 50.0 ± 3.2 [36 to 60] years; duration of hemodialysis treatment 79.6 ± 12 [34 to 133] months; these patients had very often hypotensive episodes during dialysis); and one group of normotensive dialysis patients (8 males, 1 female) with normal interdialytic blood pressure ($P_{syst} > 135$ mm Hg; blood pressure average 144.2 ± 3.6/88.4 ± 2.0 mm Hg; mean age 48.2 ± 3.8 [27 to 56] years; duration of hemodialysis treatment 24 ± 4 [6 to 41] months; blood pressure was relatively stable during dialysis). There was no difference in the mean body weight of the two groups. The age–matched control group consisted of four male and four female volunteers, mean age: 49.3 ± 5.9 (27 to 68) years; blood pressure average: 132 ± 6/74.8 ± 2.7 mm Hg. The phenylephrine test was performed always between 8.00 and 10.00 a.m. The subjects remained supine for at least 30 minutes. Thereafter bolus doses of phenylephrine were injected into the cubital vein and blood pressure was measured repeatedly by the auscultatory method (diastolic phase V). Progressively larger doses of phenylephrine were injected starting with 100 μg, until the systolic blood pressure transiently increased by 20 mm Hg. Blood pressure was allowed to return to control value before each successive injection.

To evaluate autonomic function a series of standardized clinical tests was performed in the same three age–matched groups. The tests were performed in supine position after one hour of rest always between 8.00 and 10.00 a.m.

Valsalva–maneuver

Patients were instructed to blow into a mouthpiece connected to a mercury manometer at a respiratory pressure of 40 mm Hg for 15 seconds. Heart rate was continuously recorded on an electrocardiogram throughout the maneuver and for 30 seconds after the end of the maneuver. The heart rate response to the Valsalva–maneuver was expressed as the Valsalva ratio [14], that is, the ratio between maximal bradycardia (longest RR interval) after strain release and maximal tachycardia (shortest RR-interval) during the strain period. The mean of two Valsalva ratios was used for analysis.

Sustained hand–grip test

After instruction on the use of the hand–grip dynamometer patients gripped the instrument maximally with their hand for a few seconds. The highest value of three grip contractions was taken as the maximal voluntary force. Hand–grip was then maintained at 30% of this value continuously for three minutes. Blood pressure was measured at the non-exercised arm at rest and at one minute intervals during hand–grip. Heart rate was recorded using an electrocardiogram.

Deep breathing

Subjects were instructed to breathe deeply at a rate of 6 breaths/min. Between the 20th and 50th second of deep breathing each RR-interval was determined from the automatic elec-

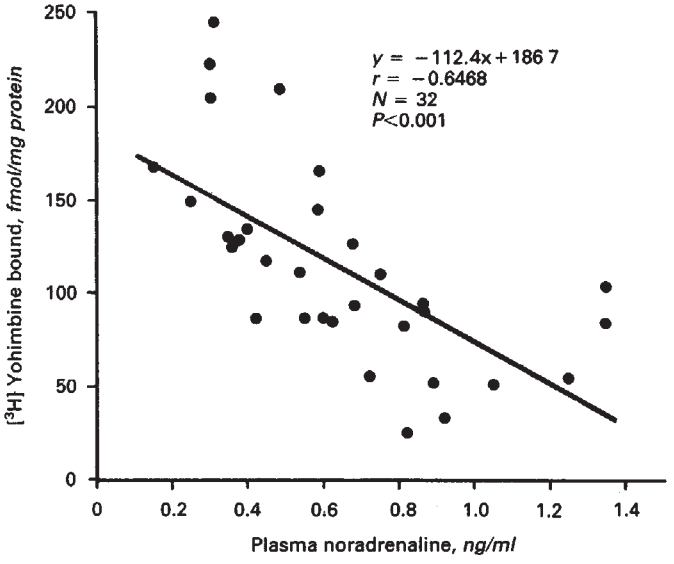

Fig. 1. *Correlation between plasma noradrenaline levels and platelet α_2-adrenoceptor density in 32 patients on maintenance hemodialysis.* Ordinate: platelet α_2-adrenoceptor density—determined by Scatchard analysis [17] of ^{3}H-yohimbine binding—in fmol ^{3}H-yohimbine specifically bound/mg protein. Abscissa: plasma noradrenaline concentrations in ng/ml.

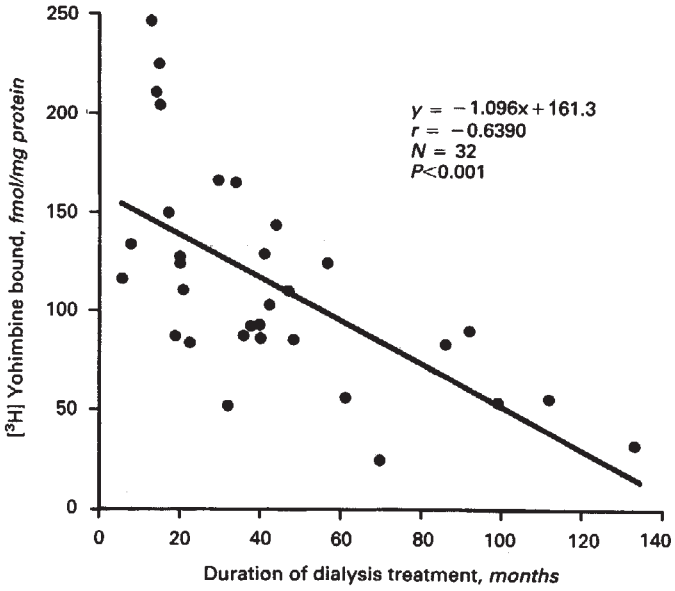

Fig. 2. *Correlation between duration of hemodialysis treatment and platelet α_2-adrenoceptor density in 32 patients on maintenance hemodialysis.* Ordinate: platelet α_2-adrenoceptor density—determined by Scatchard analysis [17] of ^{3}H-yohimbine binding—in fmol ^{3}H-yohimbine specifically bound/mg protein. Abscissa: duration of dialysis treatment in months.

trocardiographic tracings. Beat–to–beat variation was calculated as the standard deviation of the mean instantaneous heart rate over the 30 second period analyzed.

Plasma noradrenaline levels were assessed by the radioenzymatic method of Da Prada and Zürcher [15] as modified by Nagel and Schümann [16]. Protein was determined by the Lowry method using bovine serum albumin as standard.

Calculations and statistical evaluations

The experimental data given in text and figures are means ± SEM of N experiments. The maximal number of ^{3}H-yohimbine binding sites in platelet membranes and the equilibrium dissociation constants (K_D) were calculated from plots according to Scatchard [17]. Linear regression analysis of the data was performed by the least squares method. Mean arterial blood pressure (MAP) was calculated according to the equation:

$$\text{MAP} = \frac{2 \times \text{P diast} + \text{P syst}}{3}$$

The significance of differences was estimated by unpaired Student's *t*-test. A *P* value less than 0.05 was considered to be significant.

Results

Changes of platelet α_2-adrenoceptor density in patients on maintenance hemodialysis

In the 32 patients on maintenance hemodialysis the mean number of α_2-adrenoceptors in the platelets, determined by Scatchard analysis of ^{3}H-yohimbine binding, amounted to 114.3 ± 9.6 (range 25 to 247) fmol ^{3}H-yohimbine specifically bound/mg protein. In contrast to our recent observation of an age–dependent decrease in α_2-adrenoceptor density in platelets of healthy volunteers [18] platelet α_2-adrenoceptor density in the patients on maintenance hemodialysis was not related to age, but was significantly inverse correlated to the plasma noradrenaline levels (Fig. 1). In addition, both platelet α_2-adrenoceptor density and plasma noradrenaline levels were significantly related to the duration of the hemodialysis treatment: with increasing duration of treatment platelet α_2-adrenoceptor density decreased (Fig. 2), whereas plasma noradrenaline levels increased (Fig. 3). Moreover, the mean arterial blood–pressure of the patients was significantly correlated with duration of dialysis treatment, platelet α_2-adrenoceptor density, and plasma noradrenaline levels. Mean arterial blood–pressure decreased with increasing duration of dialysis treatment (Fig. 4) and increasing plasma noradrenaline levels (Fig. 5); on the other hand, it was positively correlated to the density of platelet α_2-adrenoceptors, that is the higher the density of α_2-adrenoceptors, the higher the mean arterial blood pressure of the patients (Fig. 6).

Changes in α_1-adrenoceptor function in patients on maintenance hemodialysis

In order to find out whether α_1-adrenoceptor function might also be changed in the course of dialysis treatment, the blood pressure response of healthy volunteers (mean platelet α_2-adrenoceptor density 124 ± 26 (109 to 214) fmol ^{3}H-yohimbine bound/mg protein, N = 8; mean plasma noradrenaline levels 0.42 ± 0.14 (0.16 to 0.66) ng/ml, N = 8) to i.v. injections of the selective α_1-adrenoceptor agonist phenylephrine was compared with those in dialysis patients. For this purpose the patients on maintenance hemodialysis were divided into two age–matched groups. One group had normal blood pressure (mean platelet

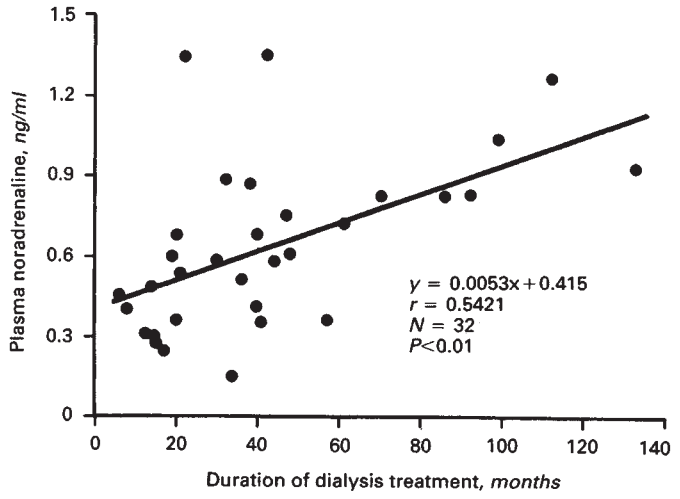

Fig. 3. *Correlation between duration of hemodialysis treatment and plasma noradrenaline levels in 32 patients on maintenance hemodialysis.* Ordinate: plasma noradrenaline concentrations in ng/ml. Abscissa: duration of dialysis treatment in months.

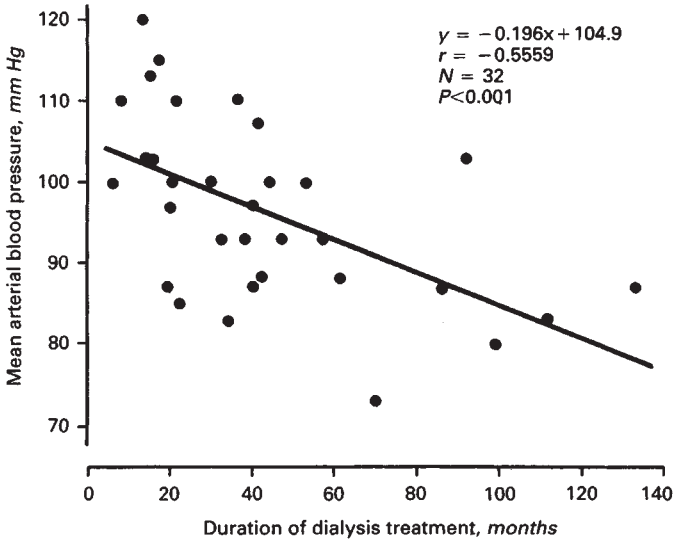

Fig. 4. *Correlation between duration of hemodialysis treatment and mean arterial blood pressure in 32 patients on maintenance hemodialysis.* Ordinate: mean arterial blood pressure in mm Hg. Abscissa: duration of dialysis treatment in months.

α_2-adrenoceptor density 135 ± 15.5 [86.7 to 209.7] fmol ^{3}H-yohimbine bound/mg protein, N = 9, mean plasma noradrenaline levels 0.48 ± 0.04 [0.35 to 0.59] ng/ml) and one group had relatively low blood–pressure (mean platelet α_2-adrenoceptor density 71.7 ± 16.3 [25 to 102.5] fmol ^{3}H-yohimbine bound/mg protein, mean plasma noradrenaline levels 0.89 ± 0.13 [0.72 to 1.35] ng/ml, N = 8). Phenylephrine increased the blood pressure in a dose–dependent manner in all three groups (Fig. 7). In healthy controls and normotensive dialysis patients the dose–response curves of phenylephrine were nearly superimposable; in the group of hypotensive dialysis patients, however, the slope of the curve was significantly reduced. Accordingly, the

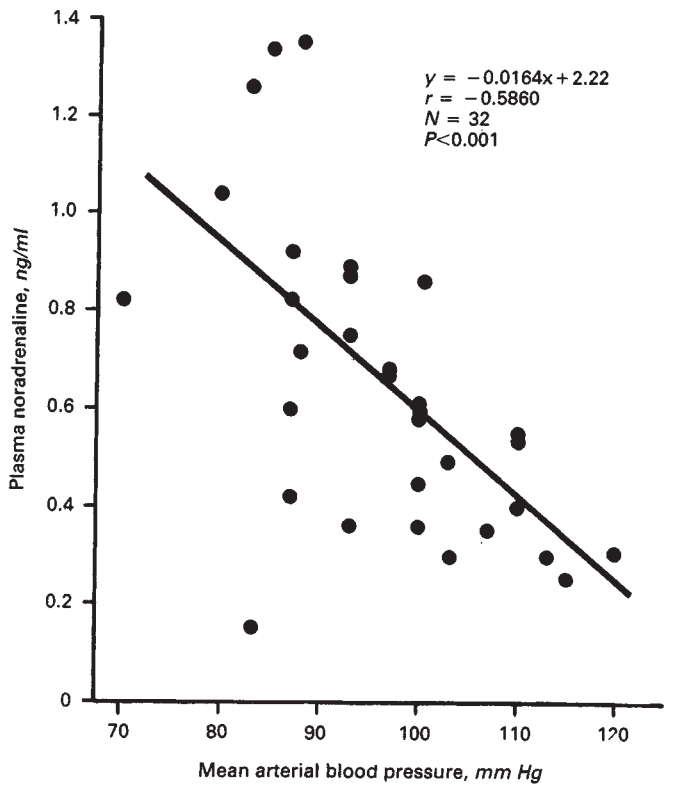

Fig. 5. *Correlation between mean arterial blood pressure and plasma noradrenaline levels in 32 patients on maintenance hemodialysis.* Ordinate: plasma noradrenaline concentrations in ng/ml. Abscissa: mean arterial blood pressure in mm Hg.

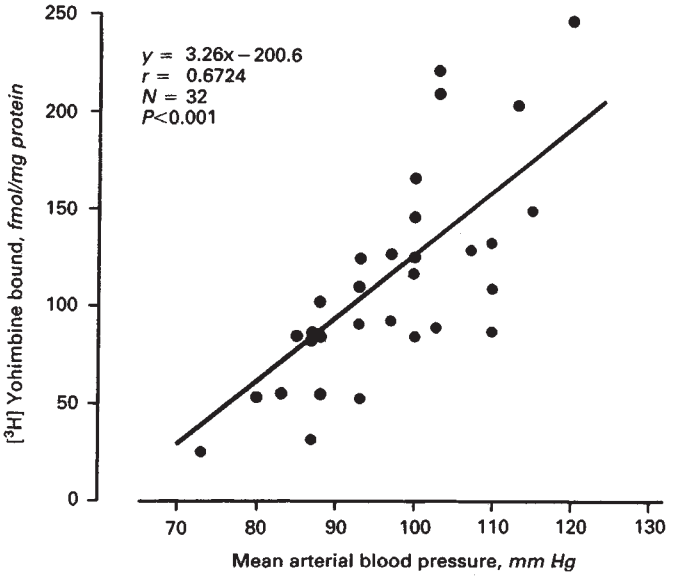

Fig. 6. *Correlation between mean arterial blood pressure and platelet α_2-adrenoceptor density in 32 patients on maintenance hemodialysis.* Ordinate: platelet α_2-adrenoceptor density—determined by Scatchard-analysis [17] of ^{3}H-yohimbine binding in fmol ^{3}H-yohimbine specifically bound/mg protein. Abscissa: mean arterial blood pressure in mm Hg.

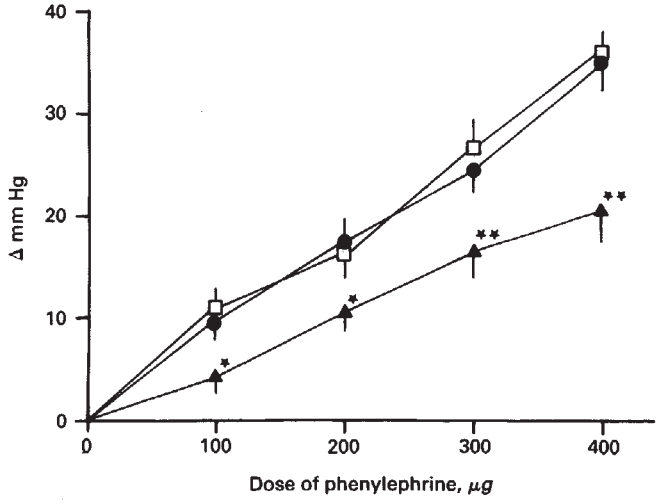

Fig. 7. *Effects of i.v. injections of phenylephrine on systolic blood pressure in 8 healthy volunteers (□——□), 9 normotensive patients on maintenance hemodialysis (●——●) and 8 hypotensive patients on maintenance hemodialysis (▲——▲).* Ordinate: Increase in systolic blood pressure in Δ mm Hg. Abscissa: Dose of phenylephrine in μg. Means ± SEM. Symbols are: ** $P < 0.01$, * $P < 0.05$ vs. normotensive controls.

EC_{20}-value of phenylephrine (the dose required to increase systolic blood pressure by 20 mm Hg) was significantly higher ($P < 0.01$) in the group of hypotensive dialysis patients (384.5 ± 48 μg, $N = 8$) than in the other two groups (control, 238.3 ± 55 μg, $N = 8$; normotensive dialysis patients, 227.6 ± 44 μg, N = 9). For all 25 patients there was an inverse relationship between the EC_{20}-values of phenylephrine and platelet α_2-adrenoceptor density, although it did not reach statistical significance ($r = -0.3235$; $0.1 > P > 0.05$).

Autonomic tests

During Valsalva–maneuver, changes in heart rate were nearly identical in normotensive dialysis patients and healthy controls, (Fig. 8A), whereas in the group of hypotensive dialysis patients the increase in heart rate during strain as well as the fall in pulse rate during the release period were significantly diminished (Fig. 8A). Accordingly the Valsalva–ratio (Fig. 8B) in hypotensive dialysis patients (1.28 ± 0.06, $N = 8$) was significantly lower ($P < 0.01$) than in normotensive dialysis patients (1.49 ± 0.07, $N = 8$) and in the control group (1.56 ± 0.08, $N = 8$). Sustained hand–grip exercise caused similar increases in systolic and diastolic blood pressure in all three groups (Fig. 9). There were no significant differences between the groups. The same holds true for sustained, hand grip–induced increases in heart rate (Fig. 9). Similarly, beat–to–beat variation—expressed as mean standard deviation of the mean instantaneous heart rate—was in all three groups nearly identical (Fig. 10); in addition, the well established age–related reduction in beat–to–beat variation [19–21] was similar in all three groups (Fig. 10).

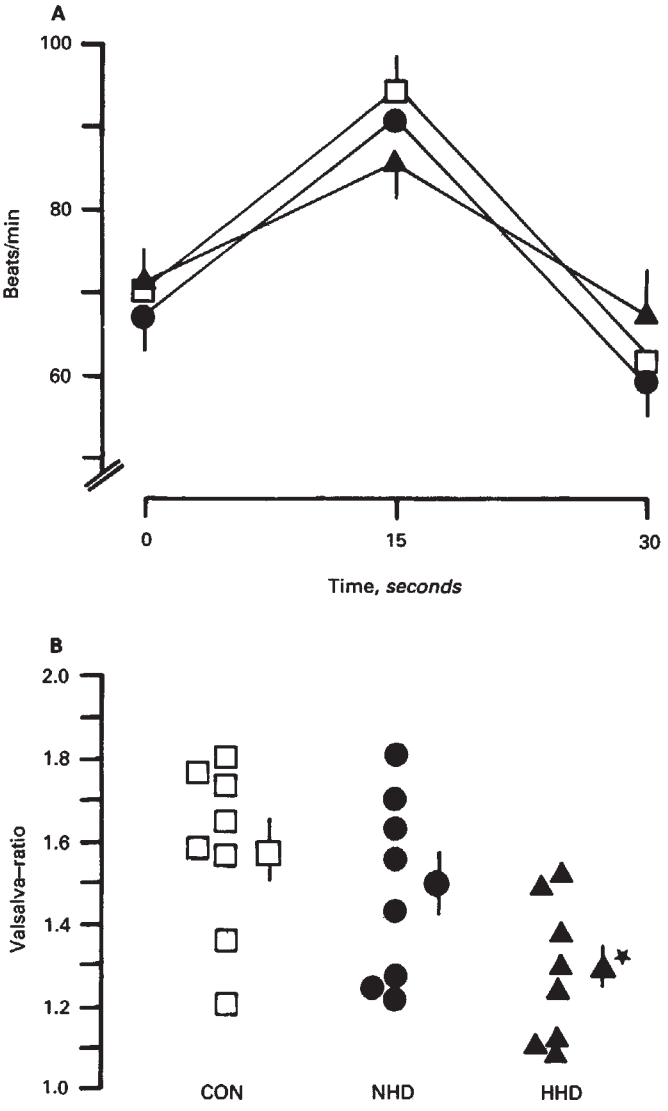

Fig. 8 A. *Heart rate before and during the Valsalva-maneuver in 8 healthy volunteers (□——□), 8 normotensive patients on maintenance hemodialysis (●——●) and 8 hypotensive patients on maintenance hemodialysis (▲——▲).* Means ± SEM. **B.** Valsalva–ratio (the ratio between the longest RR interval after strain release and the shortest RR interval during the strain period of the Valsalva-maneuver) in 8 healthy volunteers (CON), 8 normotensive patients on maintenance hemodialysis (NHD) and 8 hypotensive patients on maintenance hemodialysis (HHD). (*) Mean value of the Valsalva–ratio in the HHD-patients was significantly lower ($P < 0.01$) when compared with the normotensive controls.

Discussion

The role of the sympathetic nervous activity in blood pressure regulation in uremic patients is still poorly understood. Because of the lack of a direct measurement of sympathetic activity in humans, determination of plasma noradrenaline levels has been taken as an index for sympathetic activity. In patients with mild renal failure normal or slightly increased noradrenaline levels have been found [22]. In end–stage renal failure before initiation of hemodialysis treatment, consistently elevated plasma noradrenaline levels have been reported [23–26], which were accompanied by blunted cardiovascular responses to noradrenaline [25]. Similarly, in experimental chronic uremia in the rat plasma noradrenaline levels were elevated and vascular responses to noradrenaline were reduced [10].

Conflicting data have been reported on plasma levels of cate-

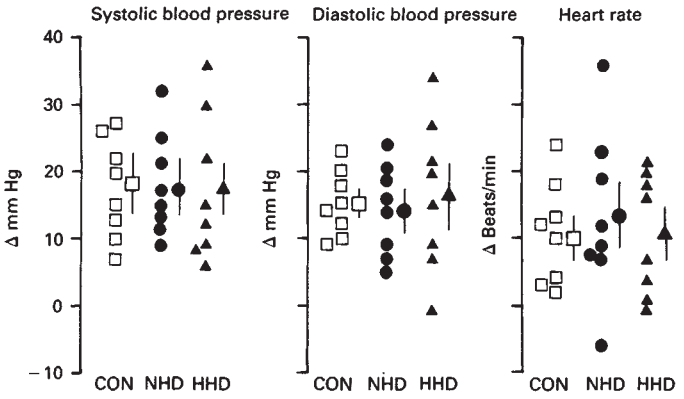

Fig. 9. *Changes in systolic blood pressure, diastolic blood pressure and heart rate in 8 healthy volunteers (CON), 8 normotensive patients on maintenance hemodialysis (NHD) and 8 hypotensive patients on maintenance hemodialysis (HHD) in response to 3 min, sustained hand–grip exercise at 30% of maximal voluntary force.* Ordinates: increase in systolic blood pressure (left panel) and diastolic blood pressure (middle panel) in Δ mm Hg and in heart rate (right panel) in Δ beats/min.

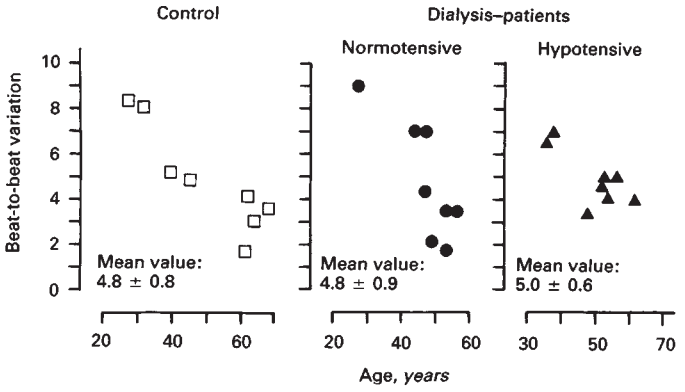

Fig. 10. *Beat–to–beat variation during deep breathing, expressed as mean standard deviation of the mean instantaneous heart rate, in relation to age in 8 healthy volunteers (control), 8 normotensive patients on maintenance hemodialysis and 8 hypotensive patients on maintenance hemodialysis.*

cholamines in patients on maintenance hemodialysis. Campese et al [25], Lake et al [27] and Kettner et al [28] found no differences in plasma noradrenaline levels between patients on maintenance hemodialysis and normal subjects; on the other hand, several groups have reported elevated plasma noradrenaline levels in patients on maintenance hemodialysis [5, 7–9, 29, 30]. The results of the present study may—at least partly—explain these discrepancies. As shown in Figure 3, the concentration of plasma noradrenaline increased significantly in the course of hemodialysis treatment. Thus, in patients who were on dialysis treatment less than two years, plasma noradrenaline levels were not significantly different from those of an age–matched control group, whereas with increasing duration of dialysis treatment plasma noradrenaline levels raised to pathological values. The mechanism underlying this increase in plasma noradrenaline levels in chronic hemodialysis patients is not known at present. However, the present results on the autonomic nervous system function in the dialysis patients—obtained by a combination of commonly used non-invasive tests [reviewed in 31] — may provide a possible explanation. As shown in Figure 8, in hypotensive dialysis patients increases in heart rate during the Valsalva–maneuver (a functional index for the overall integrity of the baroreflex arc) [32] as well as the Valsalva–ratio [14] was significantly lower than in normotensive dialysis patients and in healthy controls. On the other hand, there were no significant differences between normotensive and hypotensive dialysis patients and the age–matched healthy controls in blood pressure and heart rate responses to sustained hand–grip exercise (an index for the efferent sympathetic pathway), [33] and in beat–to–beat variation during deep breathing (an index for the parasympathetic pathway) [19]. The results are compatible with the view that during the course of long–term hemodialysis treatment the afferent pathway of the baroreflex arc might be impaired. Such a defect in the baroreflex arc could well lead to a reflex increase in sympathetic outflow and an elevation of plasma noradrenaline levels to maintain blood pressure. Another possibility could be that plasma noradrenaline levels might increase reflectorily to an (in chronic uremia persistently existing) reduced end–organ response to α-adrenoceptor stimulation caused by unknown factors (uremic toxins?), as has been demonstrated in experimental chronic uremia [10] as well as in uremic man [5, 25, 28].

In the past few years radioligand binding studies have led to a rapid progress in understanding the molecular pharmacology of α- and β-adrenoceptors. It is now apparent that a wide variety of hormones, drugs, physiological and pathological conditions may alter adrenoceptor number and, by this, the sensitivity of tissues to catecholamines [reviewed in 34, 35]. Catecholamines can regulate the concentration of their own receptors. An increase in catecholamine concentration reduces the number ("down–regulation"), while reduction in catecholamine concentration increases the number of receptors ("up–regulation") [34, 35]. Thus it might be possible that the decrease in platelet α_2-adrenoceptor density observed in the present study is caused through homologous down–regulation by the increased, endogenous noradrenaline levels.

The physiological importance of changes in α_2-adrenoceptors measured in human platelets to changes occuring in other human (solid) tissues has not been directly established. However, the properties of α_2-adrenoceptors in platelets — assessed by radioligand binding studies in vitro — are very similar to those in other peripheral and central tissues [36] including human cerebral cortex [37]; moreover, Sogabe Hashimoto and Nakashima [38] have recently demonstrated that the affinities of α-adrenergic drugs for postsynaptic α_2-adrenoceptors in dog saphenous vein mediating vasoconstriction resemble those in rat brain and human platelets assessed by ^{3}H-yohimbine binding. And finally in asympathicotonic orthostatic hypotension with low plasma noradrenaline levels, platelet α_2-adrenoceptor density was found to be markedly increased; concomitantly an exaggerated blood pressure response to i.v. injection of the α_1-adrenoceptor agonist phenylephrine was obtained [39]. Taking these results into account it might be concluded that changes in platelet α_2-adrenoceptors can be taken as representative for changes of α_2- (and/or α_1-) adrenoceptors in other (solid) tissues, for example, in the vasculature of the human being.

Accordingly, in the present study the decrease of α_2-adrenoceptor density in platelets of patients on maintenance hemodialysis (presumably caused by the increase in plasma noradrenaline concentrations) might reflect a decrease in vascular α-adrenoceptor responsiveness. This is, as shown in Figure 7, indeed the case; in patients, who were for a short period on dialysis treatment and had only slightly reduced platelet α_2-adrenoceptor density, the EC_{20}-value for the blood pressure increasing effect of phenylephrine was not significantly different from that in an age–matched, healthy control group; on the other hand, in patients who were for a rather long time on dialysis treatment and had low platelet α_2-adrenoceptor density, the slope of the dose–response curve for the blood pressure increasing effect of phenylephrine was decreased and the EC_{20}-value was nearly twice as high as in healthy controls. This clearly indicates a reduced responsiveness of vascular α_1-adrenoceptors to α-adrenergic stimulation. Since postsynaptic α_1- and α_2-adrenoceptors are involved in the maintenance of peripheral vascular resistance [40] and thus in blood pressure control, such reduced postsynaptic α-adrenoceptor responsiveness might well be one major cause for the development of hypotension in hemodialysis patients. This hypothesis is supported by the fact that in the present study the mean arterial blood pressure of the patients was *directly* correlated with the density of platelet α_2-adrenoceptors (and hence with the responsiveness of vascular α_1- and α_2-adrenoceptors). Thus, patients, who were for a long time on hemodialysis treatment, exhibit high plasma noradrenaline levels, low platelet α_2-adrenoceptor densities, low blood pressure responses to phenylephrine, and arterial hypotension. Similar results have been recently obtained by Botey et al [5] and Brech, Piazolo and Buerkle [30], who observed that in hypotensive, but *not* in normotensive hemodialysis patients, plasma noradrenaline levels were significantly higher and increments in mean arterial blood pressure during noradrenaline infusion were significantly lower than in their normotensive counterparts.

In conclusion, the present results are in favor of the idea that in patients on maintenance hemodialysis blood pressure might be regulated by an interplay of endogenous noradrenaline concentrations, vascular response to α-adrenoceptor stimulation and the duration of dialysis treatment. In the course of long–term dialysis treatment plasma noradrenaline levels increase, platelet α_2-adrenoceptors (reflecting obviously vascular sensitivity to α-adrenoceptor stimulation) decrease, and hence mean arterial blood pressure decreases. One possible cause for these alterations might be that plasma noradrenaline levels increase reflectorily to chronic uremia (persistently) existing, end–organ resistance to α-adrenoceptor stimulation caused by unknown factors (uremic toxins); this increase might initially prevent hypotension, but in the course of long–term dialysis treatment leads finally to a down–regulation of α-adrenoceptors and thus to arterial hypotension. A more likely explanation could be, however, that the primary cause of these alterations might be a dysfunction of the afferent limb of the baroreflex arc that leads to an enhanced sympathetic outflow and an increase in plasma noradrenaline levels. These increased noradrenaline levels, which initially may maintain blood pressure, induce during long–term dialysis treatment a down–regulation of (vascular) α-adrenoceptors leading finally to arterial hypotension. Both hypotheses imply that the duration of dialysis treatment seems to play an important role: in the course of long–term dialysis treatment the sensitivity of the vasculature to α-adrenoceptor stimulation is declining (obviously due to a reduction in the density of functional α-adrenoceptors), which might be one of the reasons for arterial hypotension in patients on long–term hemodialysis treatment.

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References

1. Lilley JJ, Golden J, Stone RA: Adrenergic regulation of blood pressure in chronic renal failure. *J Clin Invest* 57:1190–1200, 1976
2. Zucchelli P, Sturani A, Zuccala A, Santoro A, Degli Esposti E, Chiarini C: Dysfunction of the autonomic nervous system in patients with end–stage renal failure. *Contr Nephrol* 45:69–81, 1985
3. Pickering TG, Gribbin B, Oliver DO: Baroreflex sensitivity in patients on long–term haemodialysis. *Clin Sci* 43:645–657, 1972
4. Ewing DJ, Winney R: Autonomic function in patients with chronic renal failure on intermittent haemodialysis. *Nephron* 15: 424–429, 1975
5. Botey A, Gaya J, Montoliu J, Torras A, Rivera F, Lopez–Pedret J, Revert L: Postsynaptic adrenergic unresponsiveness in hypotensive haemodialysis patients. *Proc EDTA* 18:586–591, 1981
6. Kersh ES, Kronfield SJ, Under A, Popper RW, Cantor S, Cohn K: Autonomic insufficiency in uremia as a cause of haemodialysis–induced hypotension. *N Engl J Med* 290:650–653, 1974
7. Brecht HM, Ernst W, Koch KM: Plasma noradrenaline levels in regular haemodialysis patients. *Proc EDTA* 12:281–289, 1975
8. Henrich WL, Katz FH, Molinoff PB, Schrier RW: Competitive effects of hyperkalemia and volume depletion on plasma renin activity, aldosterone and catecholamine concentrations in hemodialyzed patients. *Kidney Int* 12:279–284, 1977
9. McGrath BP, Ledingham JGG, Benedict CR: Catecholamines in peripheral venous plasma in patients on chronic hemodialysis. *Clin Sci Mol Med* 55:89–96, 1978
10. Rascher W, Schömig A, Kreye VAW, Ritz E: Diminished vascular response to noradrenaline in experimental chronic uremia. *Kidney Int* 21:20–27, 1982.
11. Meggs LG, Ben–Ari J, Gammon D, Choudhury M, Goodman AI: Effect of chronic uremia on the cardiovascular alpha$_1$ receptor. *Life Sci* 39:169–179, 1986
12. Graben N, Daul A, Bischoff K, Klöppel A: Use of $NaHCO_3$ in acetate dialysis as an effective alternative to bicarbonate dialysis. *Prog Artif Organs* 1:548–553, 1983
13. Brodde O-E, Hardung A, Ebel H, Bock KD: GTP regulates binding of agonists to α_2-adrenergic receptors in human platelets. *Arch Int Pharmacodyn Ther* 258:193–207, 1982
14. Levin AB: A simple test of cardiac function based upon heart rate changes induced by the Valsalva maneuver. *Am J Cardiol* 18:90–99, 1966
15. Da Prada M, Zürcher G: Simultaneous radioenzymatic determination of plasma and tissue adrenaline, noradrenaline and dopamine within the femtomole range. *Life Sci* 19:1161–1174, 1976
16. Nagel M, Schümann HJ: A sensitive method for determination of conjugated catecholamines in blood plasma. *J Clin Chem Clin Biochem* 18:431–432, 1980
17. Scatchard G: The attraction of proteins for small molecules and ions. *Ann N Y Acad Sci* 51:660–672, 1949
18. Brodde O-E, Anlauf M, Graben N, Bock KD: Age–dependent decrease of α_2-adrenergic receptor number in human platelets. *Eur*

J Pharmacol 81:345–347, 1982
19. WHEELER T, WATKINS PJ: Cardiac denervation in diabetes. *Br Med J*:584–586, 1973
20. SMITH SE, SMITH SA: Heart rate variability in healthy subjects measured with a bedside computer–based technique. *Clin Sci* 61:379–383, 1981
21. GAUTSCHY B, WEIDMANN P, GNÄDINGER MP: Autonomic function tests as related to age and gender in normal man. *Klin Wochenschr* 64:499–505, 1986
22. BERETTA–PICCOLI C, WEIDMANN P, SCHIFFL H, COTTIER C, REUBI FC: Enhanced cardiovascular pressor reactivity to norepinephrine in mild renal disease. *Kidney Int* 22:297–303, 1982
23. ATUK NO, BAILEY CJ, TURNER S, PEACH MJ, WESTERVELT FB: Red blood cell catechol-O-methyl-transferase, plasma catecholamines and renin in renal failure. *Trans Am Soc Artif Int Organs* 22:195–200, 1976
24. GRÜTZMACHER P, ERNST W, SCHOEPPE W: Funktion und Aktivität des sympathischen Nervensystems bei Niereninsuffizienz. *Nieren- und Hochdruckkrankheiten* 11:122–129, 1982
25. CAMPESE VM, ROMOFF MS, LEVITAN D, LANE K, MASSRY SG: Mechanisms of autonomic nervous system dysfunction in uremia. *Kidney Int* 20:246–253, 1981
26. DARWISH R, ELIA AN, VAZIRI ND, PAHL M, POWERES D, STOKES JD: Plasma and urinary catecholamines and their metabolites in chronic renal failure. *Arch Intern Med* 144:69–71, 1984
27. LAKE CR, ZIEGLER MG, COLEMAN MD, KOPIN IJ: Plasma levels of norepinephrine and dopamine β-hydroxylase in CRF patients treated with dialysis. *Cardiovasc Med* 4:1099–1111, 1979
28. KETTNER A, GOLDBERG A, HAGBERG J, DELMEZ J, HARTER H: Cardiovascular and metabolic response to submaximal exercise in hemodialysis patients. *Kidney Int* 26:66–71, 1984
29. FREWIN DB, BARTHOLOMEUSZ FDL, CUMMINGS MF, CLARKSON AR, BARRY LA, FURBER B, DE LORENZO C, JONSSON JR, TAYLOR WB: Changes in plasma catecholamine levels during hemodialysis. *Aust NZ J Med* 14:31–34, 1984
30. BRECH WJ, PIAZOLO P, BUERKLE HR: Simple test combination to localize lesions of the autonomic pathway in hypotensive haemodialysis patients. *Proc EDTA-ERA* 22:266–269, 1985
31. WEIDMANN P: Die orthostatische Hypotonie. *Schweiz Med Wochenschr* 114:246–260, 1984
32. HENRICH WL: Autonomic insufficiency. *Arch Intern Med* 142: 339–344, 1982
33. EWING DJ, IRVING JB, KERR F, WILDSMITH JAW, CLARKE BF: Cardiovascular responses to sustained handgrip in normal subjects and in patients with diabetes mellitus: A test of autonomic function. *Clin Sci Mol Med* 46:295–306, 1974
34. MOTULSKY HJ, INSEL PA: Adrenergic receptors in man. Direct identification, physiologic regulation and clinical alterations. *N Engl J Med* 307:18–29, 1982
35. STILES GL, CARON MG, LEFKOWITZ RJ: β-Adrenergic receptors: biochemical mechanisms of physiological regulation. *Physiol Rev* 64:661–743, 1984
36. BRODDE O-E, EYMER T, ARROYO J: ^{3}H-Yohimbine binding to guinea–pig kidney and calf cerebral cortex membranes: Comparison with human platelets. *Arch Int Pharmacodyn Ther* 266:208–220, 1983
37. SUMMERS RJ, BARNETT DB, NAHORSKI SR: The characteristics of adrenoceptors in homogenates of human cerebral cortex labelled by ^{3}H-rauwolscine. *Life Sci* 33:1105–1112, 1983
38. SOGABE K, HASHIMOTO H, NAKASHIMA M: Affinities of adrenergic drugs for α_2-adrenoceptors in dog saphenous vein in comparison with those in rat brain or human platelets. *Blood Vessels* 22:127–138, 1985
39. BRODDE O-E, ANLAUF M, ARROYO J, WAGNER R, WEBER F, BOCK KD: Hypersensitivity of adrenergic receptors and blood–pressure response to oral yohimbine in orthostatic hypotension. *N Engl J Med* 308:1033–1034, 1983
40. TIMMERMANS PBMWM, VAN ZWIETEN PA: The postsynaptic α_2-adrenoceptor. *J Auton Pharmacol* 1:171–183, 1981